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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,869	07/18/2003	Suresh K. Tikoo	293102003600	2929
25226 7590 01/22/2008 MORRISON & FOERSTER LLP 755 PAGE MILL RD PALO ALTO, CA 94304-1018			EXAMINER CHEN, STACY BROWN	
			ART UNIT 1648	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/622,869

Applicant(s)

TIKOO, SURESH K.

Examiner

Stacy B. Chen

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-64 is/are pending in the application.
- 4a) Of the above claim(s) 3, 5, 7, 10, 16, 28, 40-55 and 58-64 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4, 6, 8, 9, 11, 17, 20-27, 29-39, 56 and 57 is/are rejected.
- 7) ☒ Claim(s) 12-14, 18 and 19 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 July 2003 and 22 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/9/03; 6/2/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election without traverse of Group IV, claims 2, 6, 9 and 15 with respect to motif TATTTTTT and SEQ ID NO: 8 (GGGTGTATTTTTTCCCCTCA), is acknowledged and entered. Claims 1, 2, 4, 6, 8, 9, 11-15, 17-27, 29-39, 56 and 57 are under examination. Claims 3, 5, 7, 10, 16, 28, 40-55 and 58-64 are withdrawn from consideration being drawn to non-elected subject matter. (Previously, claims 5, 28 and 58 were indicated as part of the Group elected for examination. However, upon further consideration of the elected Group IV, which comprises a sequence that belongs to PAV3, claims 5 and 28 cannot be included in the examined Group as they comprise PAV5, which does not contain the elected motif. As for claim 58, also withdrawn, it depends from claim 26 which is itself withdrawn.)

Claims Summary

2. The claims are drawn to an isolated porcine adenovirus (PAV) sequence essential for encapsidation (inserting adenovirus DNA into adenovirus capsids). The sequence comprises TATTTTTT, which is derived from PAV3 and presumed to be present in any PAV3 genome. Specifically, the sequence comprises SEQ ID NO: 8, also derived from PAV3 and is also presumed to be naturally present in any PAV3 genome. Also claimed are vectors, specifically, replication-defective vectors comprising heterologous encapsidation sequences and inverted terminal repeat sequences from human adenovirus or bovine adenovirus. The vector also comprises at least one nucleic acid sequence encoding a transgene, and the vector has a deletion in a nucleic acid sequence encoding an adenovirus protein. The transgene encodes an immunogenic polypeptide, an antigen of a pathogen (human, bovine, porcine, etc.).

In another embodiment, the recombinant PAV vector comprises a deletion of a sequence essential for encapsidation, specifically, TATTTTTT. (The specification discloses that packaging motifs of PAV3 appear to be functionally redundant, meaning that one or more encapsidation sequences can be deleted and viral DNA can still be encapsidated. The specification teaches that some of them alone can support the viral packaging and make PAV viable (page 6, paragraph [0054]).)

Also claimed are viral particles comprising the vectors, host cells comprising the vectors, and compositions comprising the vectors with a pharmaceutically acceptable carrier or excipient. The compositions are capable of inducing an immune response in a mammalian subject, or providing protection in a mammalian host against infection (vaccines).

Claim Objections

3. Claims 4 and 27 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 3 and 27 are drawn to a sequence for encapsidation and a vector comprising a deletion of a sequence for encapsidation. The elected sequence, TATTTTTT is understood be present only in PAV3. Since the elected sequence is recited in claims 1 and 26, the subject matter of claims 4 and 27 does not further limit the claims from which they depend. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell, wherein the cell is isolated, purified or cultured, does not reasonably provide enablement for a host cell comprised within a living organism such as a transgenic animal or human. It is noted that the specification contemplates gene therapy in humans (page 49, paragraphs [0146]-[0147]). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification is not enabling for host cells comprised within a subject for the reasons set forth below.

The instant specification does not teach how to overcome problems with *in vivo* delivery and expression with respect to the administration of the claimed polynucleotide vectors. The state of the art as of the priority date sought for the instant application is that *in vivo* gene delivery is not well developed and is highly unpredictable. For instance, Verma *et al.* (*Nature*, 1997, Vol. 389, pp. 239-242, herein, "Verma") teaches that the Achilles heel of gene therapy is gene delivery. Verma states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). As of the priority date sought, it was well known in the art how to infect or transfect cells *in vitro* or *ex vivo* with viral vectors. However, using viral vectors to deliver DNA to an organism *in vivo*, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an

organism *in vivo* is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of *in vivo* systems.

Although the Verma reference was published over a decade ago, the field of gene therapy remains uncertain and unpredictable. A review of gene therapy published online (and updated August 6, 2007) offers an overview of various viral vectors (Human Genome Project Information, 7 pages, www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml). Continued problems include short-lived expression, avoiding the immune system, toxicity, targeting and the complexity of working with multigene disorders (page 3).

Specifically, with regard to adenoviral vectors in gene therapy, which appear to be the most promising of all candidate viral vectors for various reasons outlined in Vorburger *et al.* (*The Oncologist*, 2002, 7:46-59, "Vorburger"), there remain unresolved issues of tissue targeting, regulation of promoter activity and transgene expression rates (pages 54-55). Vorburger notes that the only clinically efficacious adenoviral vector therapy has been with replication-competent, tumor-cell-specific adenovirus (page 55, second column, "Future Directions"). St. George *et al.* (*Gene Therapy*, 2003, 10:1135-1141) also comments on these same obstacles relating to adenovirus vectors in gene therapy.

The specification does not remedy any of the deficiencies of the prior art with regard to gene therapy. There are no working examples or relevant data relating to the use of the claimed host cells in a gene therapy experiment. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use a host cell in the gene therapy context. Amendment of claims 29-32 to recite "isolated host cell" would overcome this rejection.

5. Claims 26, 27, 30, 32, 34, 36, 38, 39 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to recombinant PAV vectors comprises a deletion of a sequence essential for encapsidation, specifically, TATTTTTT. The claims, when read broadly, encompass a PAV vector is incapable of encapsidation, an inoperative embodiment. Since the claims do not provide any requirements for the presence of other encapsidation sequences, or the presence of an entire PAV genome (or at least the part of the genome that necessarily contains other encapsidation sequences), the claims are broadly read as encompassing an inoperative embodiment. The Office recognizes that the specification discloses that packaging motifs of PAV3 appear to be functionally redundant, meaning that one or more encapsidation sequences can be deleted and viral DNA can still be encapsidated. The specification teaches that some of them alone can support viral packaging and make PAV viable (page 6, paragraph [0054]).) However, the claim language encompasses an embodiment wherein none of the sequences required for encapsidation are present.

6. Claims 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to

vaccines comprising a replication-defective adenoviral vector (having TATTTTTT) and a recombinant porcine adenovirus vector comprising a deletion of TATTTTTT. The claims are not enabled by the specification for their ability to prevent any disease upon challenge with an infectious agent/pathogen.

The breadth of the claims encompasses a vaccine that presumably prevents a given disease upon challenge. The nature of the invention is replication-competent adenovirus vectors that carry a gene of interest that will be expressed *in vivo* and induce an immune response effective to prevent disease. Another aspect of the nature of the invention is a porcine adenovirus vector having a deletion in one of the encapsidation sequences that carries a gene of interest that will be expressed *in vivo* and induce an immune response effective to prevent disease. (Note that the claims do not even require the presence of any gene of interest that will encode a protein or peptide against which an immune response is desired.)

With regard to PAV3 vectors inducing an protective immune response against PAV3, or any other adenovirus, the specification does not provide data that shows protective efficacy in an acceptable animal model. There is no evidence of cross-protection across different types of PAV, nor cross-protection across other animals.

With respect to replication-defective adenovirus vectors, there does not appear to be any literature relating to vaccines (successful) using such constructs. As disclosed in Vorburger, the only clinically efficacious adenoviral vector therapy has been with replication-competent, tumor-cell-specific adenovirus (page 55, second column, "Future Directions"). Art relating to replication-competent adenovirus (RCA) vectors is represented by Demberg *et al.* (*J. Virology*, 2007, 81(7):3414-3427, "Demberg") and Barton *et al.* (*Molecular Therapy*, 2006, 13(2):347-356,

“Barton”), for example. Demberg discloses the construction of RCA vectors (adenovirus 5, Ad5) carrying HIV tat and env sequences, similar to the RCA vectors carrying SIV tat and env previously constructed by Demberg (abstract). Although the construct showed protective immunity in the SHIV model, it must be noted that protection against HIV in humans using such a construct is highly unpredictable because the SHIV model is deficient in that the monkeys cannot be challenged with HIV, a major drawback of the SHIV model. Barton discloses second-generation replication-competent oncolytic adenovirus model having improved suicide genes and an ADP gene (abstract). Barton teaches that replication-competent oncolytic adenoviruses alone, as therapeutic agents, are not sufficiently active as first-line cancer therapy (page 347, first column).

Given the breadth of the claims, the nature of the invention, the high level of skill in the art, the low level of predictability, the state of the art, and the lack of working examples, it would require undue experimentation for one of skill in the art to make vaccines with the claimed constructs. Protective efficacy must be demonstrated with challenge experiments in acceptable animal models.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Nielsen et al. (US 6,350,853, "Nielsen"). The claims are drawn to an isolated porcine adenovirus sequence essential for encapsidation comprising TATTTTTT from PAV3. The Nielsen reference discloses a sequence of 10 nucleotides that contains TATTTTTT (see Nielsen's SEQ ID NO: 4). Although Nielsen does not disclose SEQ ID NO: 4 as a PAV3 sequence essential for encapsidation, the claims are drawn to products, regardless of the name, origin or function assigned to it. Therefore, Nielsen's sequence anticipates Applicant's invention as claimed in claims 1 and 4.

8. Claims 1, 2, 4, 6, 8, 9, 11, 15, 17, 29, 31, 33, 35, 37, 38, 39 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Reddy *et al.* (WO 99/53047, "Reddy"). The claims are summarized above. (Note that the claims are rejected for their structural components and not for their non-enabled use as a vaccine or in a method of gene therapy.) Reddy discloses the complete nucleotide sequence of the genome of PAV3, which inherently contains TATTTTTT and SEQ ID NO: 8 (abstract). The genome is used as a vector for expression of heterologous nucleotide sequences, including immunogenic subunits of pathogens (abstract). The vector is also disclosed as being useful for gene therapy purposes (abstract) or gene immunization purposes in combination with pharmaceutical carriers/adjuvants (pages 30-31). Reddy teaches that non-essential regions of the PAV vector may be deleted for inserting heterologous sequences (page 5, first paragraph). Also disclosed are replication-defective recombinant PAV viruses (page 5, last paragraph). Therefore, the claimed subject matter is anticipated by Reddy.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 6, 8, 9, 11, 17, 20, 22-25, 29, 33, 35, 37, 39 and 56 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 and 19-23 of U.S. Patent No. 6,492,343. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to a species of the instantly claimed genus. Although the patented claims do not specifically mention the presence of TATTTTTT or SEQ ID NO: 8, the PAV3 nucleotide vector of the patent inherently contains these sequences. The patented claims are a species of the instant genus claims because the patented claims specify where the nucleotide insertion occurs, whereas the instant claims do not.

Conclusion

10. Claims 12-14, 18 and 19 are objected to for being dependent on rejected claims.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B. Chen/ 1-17-2008
Primary Examiner, TC1600